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Review Article

Effects of ascorbic acid on chemical and thermal corneal burns: a comprehensive literature review

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ABSTRACT

Background: Ascorbic acid has been suggested to be effective against chemical burns. It was first tested in rabbits before being implemented in human subjects. It was proven to be useful in treatments for different conditions, such as corneal chemical and thermal burns. Herein, we aimed to review the effects of ascorbic acid in the healing of chemical and thermal corneal burns.
Methods: We performed an electronic search of English literature in MEDLINE, clinicaltrials.gov, and Google Scholar, without time constraints. Articles were selected based on inclusion and exclusion criteria, using they keywords "Corneal Burn," AND "Corneal Ulcer," AND "Vitamin C." This yielded 17 English language articles focused on the effect of vitamin C on chemical or thermal corneal burn-induced ulcers.
Results: The 17 eligible studies that fulfilled the inclusion criteria included three retrospective, nonrandomized, comparative studies on human subjects and 14 in vivo, laboratory-based studies on rabbits (12 studies), rats (one study), as well as guinea-pigs (one study). Most studies showed benefits in using vitamin C as a prophylactic treatment to delay or stop corneal ulcer formation after chemical or thermal corneal burn.
Conclusions: Vitamin C is a very basic, inexpensive prescription and can be used to treat corneal ulcers following a variety of corneal burns. This review highlights the necessity for conducting randomized controlled trials to investigate the prophylactic role of vitamin C and to determine its minimum required dose for the management of corneal ulcers after different types of corneal burns.

KEY WORDS

corneal ulcer, corneal burns, vitamin C, MEDLINE, clinical trials

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INTRODUCTION

Vitamin C or ascorbic acid has been shown to offer protection against immune system defects [1-3], cardiovascular disease [4, 5], maternal health problems, eye disease, and skin wrinkling [6-8] are among the advantages of vitamin C. Vitamin C has been demonstrated to have potent antioxidant [4], antitumor, [2] and antiviral activities [9-11]. Since 1946, as the first research on this topic, ascorbic acid has been proposed to be an effective modality for treating corneal chemical burns [12-17]. Initially, the effects of vitamin C were examined in rabbits, and the findings were later implemented in human subjects. The results showed promising effects in the treatment of corneal chemical burns [18]. One randomized clinical trial showed that a high dose of vitamin C improved the patients' ventricular function after coronary artery bypass surgery.

A high dose was defined as 5 g of intravenous vitamin C and 5 g of vitamin C in a cardioplegic solution [5]. According to U.S. Food and Nutrition Board the current recommended dietary intake of 45 milligrams (mg) a day of vitamin C for adults is expected to be changed to the minimum dietary intake [19] as this dose is sufficient to prevent scurvy [19]. However, the current recommended dietary allowance or RDA for adult, non-smoking men and women, is 60 mg/day, and this exactly addresses a mean requirement of 46 mg/day to prevent scurvy deficiency [20]. Ascorbic acid was proven to be useful in treatments for different conditions, such as corneal chemical and thermal burns. This review aimed to assess the role of ascorbic acid in the healing of chemical and thermal corneal burns and to discuss the optimal dose for preventing corneal ulcers as presented in the literature.

METHODS

This review included an electronic search of MEDLINE, clinicaltrials.gov, and Google Scholar, with language limited to English but without time constraints, using the keywords 'Corneal Burn', AND 'Corneal Ulcer', AND 'Vitamin C'."

RESULTS

The search yielded 17 eligible studies that fulfilled the inclusion criteria. The 17 selected articles included three retrospective, nonrandomized, comparative studies on human subjects and 14 in vivo, laboratory-based studies. The details of these studies are outlined in Table 1. Most studies showed benefits of using vitamin C as a prophylactic treatment that delays or stops corneal ulcer from developing after corneal burns.

Alkali Burn: Levinson et al. showed that exogenous maintenance of sufficient aqueous humor levels of ascorbic acid could resolve the comparatively scorbutic state of the anterior segment following an alkali burn of 12 mm in rabbit eyes, thus reducing the development of corneal ulceration and perforation [21]. Pfister and Paterson reported that their data strongly suggested that alkali-burned rabbit cornea is a localized scorbutic tissue, because corneal ulceration and perforation may develop following a severe drop in the synthesis of corneal collagen in the face of denatured collagen resorption. Ulceration may be avoided if aqueous humor ascorbate is retained at over 15 mg per 100 mL (mg/100 mL) for 24 h after parenteral administration [22]. Pfister et al. showed that two drops of 10% topical ascorbate administered hourly for 14 h of the day significantly reduced the occurrence of ulcer development after experimental alkali burns in rabbit eyes [23]. Pfister and Paterson stressed the importance of vitamin C and indicated that the development of corneal ulceration may be related to fibroblasts failing to produce sufficient collagen, which requires vitamin C, to repair the lesion [24]. Treatment with vitamin C may be administered 24–48 hours after the burn, with a dosage of topical drops 14 times daily to derive benefit. Furthermore, simultaneous oral and topical routes of medication may yield the greatest benefits [38].

Table 1. Summary of the 17 articles on the effect of ascorbic acid on thermal or chemical burn-induced corneal ulcers included in this review.

N	Author & date	Type of Study	Type of Burn	Route of Administration
1	Levinson et al., 1976 [21]	Experimental (Rabbit)	Alkali Burn	Subcutaneous
2	Pfister and Paterson, 1977 [22]	Experimental (Rabbit)	Alkali Burn	Parenterally Subcutaneous
3	Pfister et al., 1978 [23]	Experimental (Rabbit)	Alkali Burn	Topical
4	Pfister and Paterson, 1980 [24]	Experimental (Rabbit)	Alkali Burn	Parenteral or Topical
5	Pfister et al., 1981 [25]	Experimental (Rabbit)	Alkali Burn	Topical
6	Pfister et al., 1982 [26]	Experimental (Rat)	Alkali Burn	Topical
7	Reim et al., 1982 [27]	Experimental (Rabbit)	Alkali Burn	Subcutaneous
8	Petroutsos et al., 1984 [28]	Experimental (Rabbit)	Alkali Burn	Topical
9	Pfister et al., 1988 [29]	Experimental (Rabbit)	Alkali Burn	Topical
10	Pfister et al., 1991 [30]	Experimental (Rabbit)	Alkali Burn	Topical
11	Wishard and Paterson, 1980 [31]	Experimental (Rabbit)	Alkali and Acidic Burn	Subcutaneous
12	Campbell and Ferguson, 1950 [32]	Experimental (Guinea-pigs)	Thermal Burn	Orally
13	Pfister et al., 1981 [33]	Experimental (Rabbit)	Thermal Burn	Parenterally, Subcutaneous
14	Phan et al., 1985 [34]	Experimental (Rabbit)	Thermal Burn	Topical and Systemic
15	Beare, 1990 [35]	64 Patients	Chemical Burn	Topical
16	Saini and Sharma, 1993 [36]	102 Patients	Chemical Burn	Systemic
17	Brodovosky et al., 2000 [37]	121 Patients	Alkali Burn	Topical

Pfister et al. demonstrated that topical citrate has the most beneficial effect on the occurrence of corneal ulceration and perforation after alkali burn [25]. Pfister et al. also established that 10% topical ascorbate does not significantly alter the results of existing corneal ulcers in the absence of perforation in rats [26]. Reim et al. showed that systemic ascorbate therapy did not improve the rate of corneal epithelium healing, but improved levels of adenosine triphosphate (ATP) and diphosphate (ADP), and the ATP/ADP ratio, and reduced glutathione [27].

Petroutsos et al. () showed that ascorbic acid therapy significantly reduced the incidence of corneal ulcerations and perforations in rabbits compared to the control group that received sorbitol, buffer, parabens, and thimerosal-containing vehicle. These results confirmed those of previous studies and strongly suggested that a 2% ascorbic acid ophthalmic solution has potential for use in human eyes with alkali burns [28].

Pfister et al. studied corneal alkali injuries that resulted in an experimental model of induced anterior, middle, or posterior corneal ulcers. They showed that both citrate and ascorbate/citrate had a positive effect on the depth of the corneal ulcer injury due to the reduced number of perforations and improved stability in both treatment groups [29].

Pfister et al. studied whether the combined treatment with topical citrate and ascorbate had additional therapeutic value compared with citrate alone in alkali-injured rabbit eyes. In two groups of animals, two drops of 10% citrate were instilled every hour and two drops of 10% citrate together with 10% ascorbate were instilled every hour for 14 hours per day. They reported significantly fewer ulcerations in the citrate/ascorbate group during the experiment as compared with the group receiving citrate alone [30].

Brodovsky et al. showed that grade 1 or grade 2 human alkali injuries do not benefit from ascorbate and citrate treatment. In comparison, grade 3 alkali burns recovered easily, and their visual outcome was better with ascorbate and citrate treatment, whereas grade 4 burns did not show any difference [37].

Acidic Burn: Our literature search yielded only three articles on ocular acidic burns and vitamin C, indicating a need for more articles and clinical trials concerning this sight-threatening entity. Wishard and Paterson showed that subcutaneous injection of 1.5 grams/10 mL vitamin C per day into extremely acid-burned corneas in rabbits significantly restored ascorbate levels in the aqueous humor, and effectively prevented the incidence of corneal ulceration and perforation following acid burn. The group also postulated that the mechanism was similar to that observed in alkali-burned eyes [31]. Beare showed that severe chemical eye burns remained poor even following administration of ascorbate and steroid treatment [35].

Saini and Sharma studied the clinical and demographic profiles of ocular burns in India [36]. The group recommended systemic administration of high-dose ascorbic acid (6–8 g/day) [36].

Thermal Burn: We also identified only three articles on thermal burns and vitamin C [32-34], indicating the need for further research and clinical trials in this field. Campbell and Ferguson noted that corneal neovascularization is caused by ascorbate deficiency. Their findings indicated that ascorbic acid deficiency increased the occurrence of corneal vascularization after injury [32]. Pfister et al. concluded that parenteral ascorbate administration had little positive effect on tensile strength in corneal wounds in rabbit eyes. Subcutaneous ascorbate, on the other hand, had a very beneficial effect on corneal wound tensile strength in eyes with depressed aqueous humor ascorbate levels [33]. Phan et al. showed that, in contrast to chemical burn-induced corneal ulcers, in rabbits with thermal burn-induced ulceration that were treated with both topical and systemic ascorbic acid, the incidence of ulceration remained unchanged, the occurrence of perforation was enhanced, and healing was not accelerated. The onset of ulceration following thermal burn was accelerated after systemic administration of ascorbic acid [34].

DISCUSSION

The findings of the most aforementioned studies demonstrated that vitamin C has a protective effect on chemical and thermal burn-induced corneal ulcers, yet one suggests its detrimental effects in enhancing ulceration following corneal thermal burn. However, many of the studies were experimental investigations, with only a few human studies. This highlights the necessity of conducting randomized clinical trials (RCTs) on the use of vitamin C administration as a preventive measure for thermal and chemical-induced corneal ulcers. The mechanism underlying corneal burns involves penetration of cell membranes by alkaline substances or acidic substances. Alkaline substances can penetrate cell membranes

because of their lipophilic properties. They dissociate in the ocular surface into hydroxyl ions and cations. The hydroxyl ion saponifies cell membrane fatty acids, whereas the cation interacts with stromal collagen and glycosaminoglycans (GAGs). This interaction enables deeper penetration within and through the cornea, into the anterior segment. Subsequent hydration of the GAGs results in stromal haze. Corneal haze mostly appears after trauma, and is caused by inflammatory cell activation [39, 40]. On the other hand, acidic compounds, which are defined as those with pH < 4, create a barrier by binding to tissue proteins [41].

Corneal haze corresponds to the severity of the chemical burns and prognosis, according to the modified Hughes classification by Ballen and Roper-Hall [13]. They defined the severity of the chemical burn using four grades. Grade 1 was defined as having corneal epithelial damage, with no corneal haze and limbal ischemia, together with a good prognosis. Grade 2 was defined as some corneal haze but visible iris details, limbal ischemia in less than one-third, and a good prognosis. Grade 3 has a guarded prognosis and is defined as total epithelial loss, stromal haze obscuring iris details, and ischemia between one-third and half of the limbus. Grade 4 has a poor prognosis and manifests as an opaque cornea, invisible iris or pupil details, and ischemia affecting more than half of the limus [42].

When corneal injury extends through the stroma, the number of keratocytes increases, and some are stimulated to become myofibroblasts (Figure 1). Keratocytes are specialized fibroblasts that help maintain stromal integrity. Keratocytes produce collagen, GAGs, and matrix metalloproteinases (MMPs). Therefore, precise organization of collagen fibrils within the corneal stroma is essential for the maintenance of corneal clarity and proper stromal hydration. Keratocyte apoptosis is the first stromal event following epithelial injury. Soluble epithelium mediators cause cell death via apoptosis of stromal keratocytes, while other keratocytes are transformed into fibroblasts and myofibroblasts. Keratocytes also increase the production of chemokines that attract other inflammatory cells from the limbal blood supply and tear film to the stroma. Corneal stromal myofibroblasts are thought to be derived from keratocytes through the influence of transforming growth factor (TGB-β) and platelet-derived growth factor (PDGF). Corneal stromal myofibroblasts create a temporary extracellular matrix (ECM), which is essential for collagen and ECM remodeling, as well as for the formation and regression of corneal haze (Figure 1) [43]. Due to injury, dystrophy, or elevated levels of MMP-2 and MMP-9, there is a delay in the regeneration of the epithelial basement membrane (EBM) that enables TGF-β and PDGF to continue entering the corneal stroma from the epithelium, which promotes myofibroblast generation. The ongoing presence of myofibroblasts can result in an extensively disorganized ECM that adds to corneal opacity and scarring. Finally, myofibroblasts may also prevent the proper restoration of the anterior stromal keratocyte population, which is essential for full recovery of EBM. EBM restoration requires stabilization of stromal levels of TGF-β and PDGF, disappearance of myofibroblasts, repopulation of keratocytes, clearing of abnormal ECMs, and restoration of corneal clarity (Figure 1) [44].

Collagen hydration triggers fibril distortion and shortening, resulting in trabecular meshwork changes that, in effect, cause increased intraocular pressure (IOP), which can be long-lasting. Furthermore, the inflammatory mediators produced through this cycle induce the release of prostaglandins, which can also enhance IOP [39, 40, 45] It has been reported that the acid-burn mechanism is similar to in alkali-burned eyes [31]. The mechanism underlying corneal perforation due to deficiency of ascorbic acid is thought to involve the following mechanisms. Pfister et al. (1978) defined it as a lack of collagen production due to failure of fibroblasts to produce collagen for repair [23]. Pfister et al. (1980) reported that the collagen synthesis cycle decreases when ascorbic acid is deficient in the face of continued collagenase activity [24].

It has been proposed that there could be a localized area around the site of corneal collagen regeneration where the level of ascorbic acid falls below the optimal level for rapid healing. Increasing the ascorbic acid level with massive doses increased the local collagen replacement rate [47]. Few drugs support repair and minimize ulceration; however, ascorbic acid and collagenase inhibitors have been shown to support repair and minimize ulceration [48]. Ascorbate is an essential water-soluble vitamin that is a cofactor of collagen formation in the rate-limiting step. The production of collagen fibrils by fibroblasts consists of six steps, as illustrated in Figure 2. Procollagen chains are synthesized in the endoplasmic reticulum (ER) and are combined by interactions between the C-propeptides and fold to form a rod-like triple-helical domain flanked by globular N- and C-propeptides. Post-translational modifications in the ER include removal of the N- and C-propeptides from fully folded procollagen immediately after transport of procollagen across the

Golgi stacks, producing collagen molecules that can be assembled into fibrils. Covalent crosslinks occur in fibrils within and between triple-helical collagen molecules. The fibrils are indeterminate in length, insoluble, and form elaborate three-dimensional arrays that transverse numerous cell lengths [46]. Ascorbic acid is required during ribosomal collagen synthesis as a cofactor for proline hydroxylation [24]. Ascorbate supplementation by restoring depleted aqueous ascorbate levels decreases the incidence of corneal thinning and ulceration. Oral ascorbate (2 g/day) and topical 10% solutions formulated in artificial tears were effective [48]. Collagenase inhibitors that inhibit collagenolytic activity promote wound healing, thus preventing ulceration of the epithelial tissue. Several collagenase inhibitors have been reported to be effective, including cysteine, acetylcysteine, and citrate. The only commercially available collagenase inhibitor is 10–20% acetylcysteine (Mucomist) [48].

Singh et al. emphasized that improvements in understanding the pathophysiology of chemical ocular injury, such as the use of topical ascorbate and citrate, have contributed to better treatment [48].

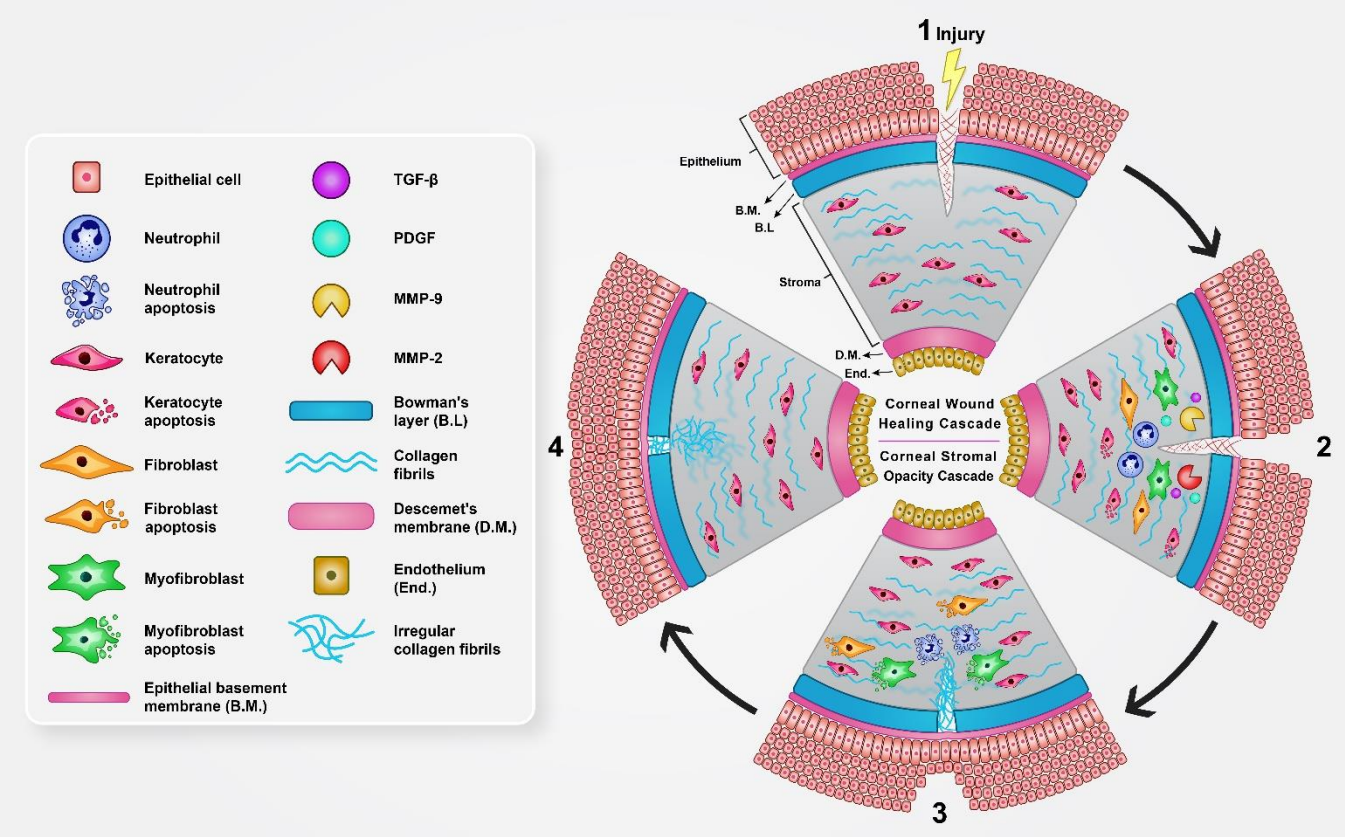

Figure 1. Corneal wound healing cascade. The process of corneal wound healing is initiated following epithelial injury (1), with subsequent apoptosis and necrosis of keratocytes, followed by primary epithelial healing (2). The proliferation and migration of keratocytes, the differentiation and migration of myofibroblasts, and the infiltration of inflammatory cells are the next stages of the wound healing cascade (2). Eventually, stromal remodeling and epithelial surface closure occur, followed by myofibroblast and inflammatory cell apoptosis and necrosis (3), and return of keratocytes to their normal state (4). Corneal stromal opacity cascade: Keratocytes, though the influence of transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDFG) form myofibroblasts, which lay down a provisional extracellular matrix (ECM). The epithelial basement membrane (EBM) degenerates due to matrix metalloproteinase-2 (MMP-2) and MMP-9, allowing TGF-β and PDFG to continue entering the corneal stroma from the epithelium (2), which promotes myofibroblasts generation (2,3). The ongoing presence of myofibroblasts lead to abundant, disorganized ECM, which contributes to corneal opacity and scarring (4). [43, 44]

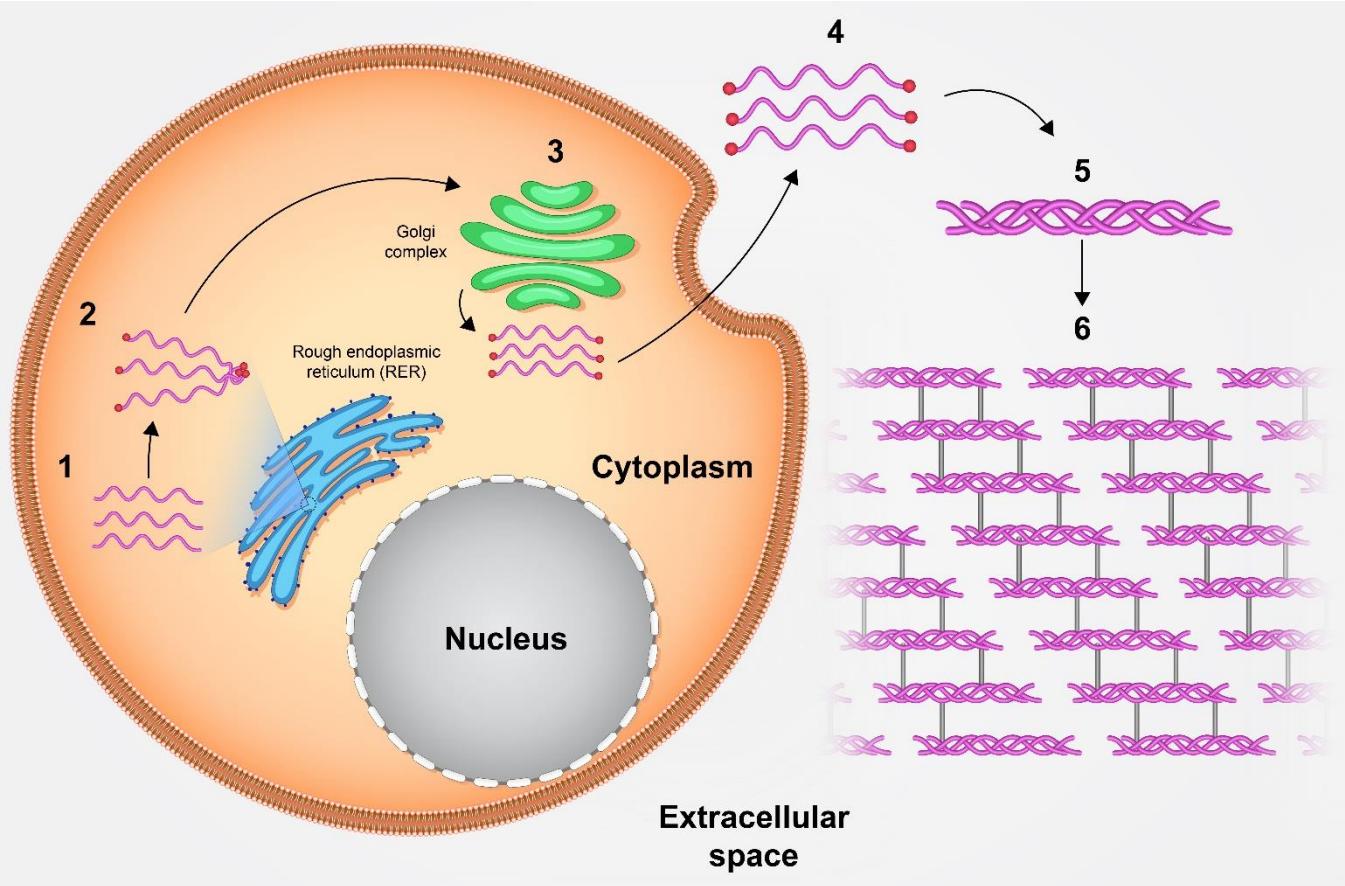

Figure 2. Summary of the steps involved in the production of collagen fibrils by fibroblasts (1): Chains synthesized in the rough endoplasmic reticulum (RER). (2): Interactions between C-propeptides and folding to form a rod-like helical domain, flanked by globular N- and C-propeptides in the RER. (3): Transport of procollagen across the Golgi stacks. (4): Procollagen trimer (removal of N- and C- propeptides by N-proteinase and C-proteinase) in the extracellular space. (5): Collagen molecule formation. (6): Collagen molecules assemble into fibrils by covalent crosslinks that occur within and between triple-helical collagen molecules [46].

On the other hand, Brodovsky et al. performed a retrospective, nonrandomized comparative study of 121 patient records with alkali burns over an 11-year period. This study evaluated the clinical outcomes of eyes treated with the traditional alkali burn care regimen, which included intensive topical steroids, ascorbate, citrate, and antibiotics, compared to eyes treated conservatively with antibiotics and a short course of steroids. Depending on their results, patients with grade 1 or grade 2 injuries did not benefit from intensive treatment with ascorbate and citrate. A tendency for faster healing and a better final visual outcome was clear in grade 3 burns, but their standard protocol did not make any difference in grade 4 burns [37]. The main limitation of this study was that we included only articles written in the English language. The strength of this review integrates the information in this subject and highlighted that most of the experiments were old and there was little new evidence available on this sight-threatening topic. We propose that further RCTs should be conducted on the use of vitamin C for chemical or thermal ocular burns, to shed light on the management of this sight-threatening entity and to determine the optimal route of administration and dosage of vitamin C.

CONCLUSIONS

Vitamin C is a basic, inexpensive prescription that can be used to treat corneal ulcers that are induced by various types of corneal burns. Further randomized controlled trials and prospective studies are required to support the prophylactic and therapeutic effects of vitamin C in corneal ulcers and corneal burns and to determine the optimum dose of vitamin C. However, little is known about the effects of ascorbic acid on corneal ulcer development after either thermal or alkali burns. This gap in knowledge needs to be filled by laboratory experiments and/or clinical trials. Finally, vitamin C should not be used as an independent mode of treatment, but it could be an adjunctive treatment in the management of thermal or chemical-induced corneal ulcers.

ETHICAL DECLARATIONS

Ethical approval: This study was a review, and no ethical approval is required.

Conflict of interest: None.

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